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ORIGINAL MEMOIRS.

MULTIPLE CARCINOMATA FOLLOWING CHRONIC X-RAY DERMATITIS.*

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The recent death of Prof. Finch of Chicago from metastatic X-ray carcinoma leads me to report in detail the history and present condition of another case of multiple epithelial carcinomata which has been under my care since 1897.

In delaying this report until the present time I have been greatly influenced by my personal regard for the patient; but the above case, the fourth fatal one in the United States, and a slowly increasing list of undoubted instances of X-ray carcinoma, here and abroad, makes it imperative that the attention of dermatologists and surgeons should be thoroughly aroused to the great danger of *all persistent X-ray ulcerations* and especially to those which have followed, with a few years interval, the chronic skin lesions of the earliest operators.

The first published account of the injurious effects of the X-ray with which I am familiar, was a paper by Marcuse,

* Read by title at a meeting of the American Surgical Association held at Washington, May, 1907.

"Dermatitis und Alopecia nach Durchstrahlung mit Röntgenstrahlen" in the *Deutsche med. Wochenschrift*, No. 30, 1896.

From 1897 the literature of this subject has grown each year. The earlier articles dealt with the immediate effects of the X-rays, dermatitis and burns; then it soon became recognized that these lesions were most excruciatingly painful and extremely slow to heal; further experience showed that some lesions closed with great difficulty only to break down again and again, and finally formed chronic ulcers;—then came the first report of cancer developing in a chronic ulcer, and finally the first death from metastatic carcinoma.

In an excellent article written by Dr. Richard Mühsam, and published in the *Archiv für klinische Chirurgie*, 1903, No. 74, "Über Dermatitis der Haut nach Röntgenbestrahlung" may be found a full bibliography of the literature up to that time and a brief résumé of the histology of the characteristic lesions with which we are unfortunately too familiar.

CASES OF X-RAY CANCER.

I and II.—In 1903 Sirk reported two cases, both in X-Ray operators, the first, after years of severe changes in the skin of the arm, neck and face, finally developed an ulcer upon the back of the hand, which soon took on the typical appearance of a carcinoma, and required amputation at the shoulder joint.

The second, with similar skin lesions of six years duration, also developed a chronic ulcer on the hand, which was excised and showed upon microscopic examination the typical picture of a skin carcinoma, with cancer nodules in the cutis—the material from these rashes was examined by Unna.

III.—Dr. illarker of England, mentioned in *Medical Record*, Oct. 22, 1904, for a long time suffered from an X-ray burn of the hand which was neglected till the cancer which had developed had extended up the arm and involved the axillary glands, when it was too late for operation.

IV.—Clarence Daly. Personal communication from Dr. Samuel Lloyd of New York and Dr. W. B. Graves of East Orange, N. J.

This patient was very seriously burned on both hands years before, in working with X-Ray tubes. He was treated at many different hospitals. Skin grafting was tried without result, until finally epithelioma developed on the right hand and on the base of the little finger of the left hand. At the time of Dr. Lloyd's first examination the right hand was infiltrated with carcinoma and the axillary glands were involved.

The arm was amputated at the shoulder joint and the glands above and below the clavicle removed. Amputation of the left hand was advised but refused. This was August 8, 1902. The ulceration gradually increased in size and depth and the left arm was amputated by Dr. Graves on March 16, 1904. Death followed from mediastinal recurrence in October, 1904.

V.—Epithelioma of finger of X-ray machine manufacturer (communication from Dr. Lloyd).

VI.—Personal communication from Dr. W. B. Coley, Surgeon of Rochester, New York. For five years had been using X-Rays continuously. Ulcerations present for six months on the backs of both hands, symptoms from which were examined by Dr. Welch and found to be malignant epithelioma. Amputation of right hand above wrist and thorough excision of ulceration on left hand October 10, 1904. Subsequent recurrence in axilla and death.

VII.—Bertha Frishman, San Francisco, death. Quotation from New York Sun, April 24, 1907.

VIII.—Foulerton's Case. *Lancet*, May 6, 1905. At a meeting of the Pathological Society of London, Foulerton reported the case of a surgeon who began systematic work with the X-rays in 1897. In May, 1903, had a severe attack of dermatitis, blistering of the skin on back of index and middle fingers of left hand, ulcers resulting healed in about four months. New skin was thin and tender and showed avoid looking pectoral. The nails fell out and very ones were hard and brittle. In December, a second attack of dermatitis again raised ulcers on first and second fingers. Ulcers on index finger remained open and in April, 1904, began to assume a malignant character. In September of that year, finger was amputated at the metacarpophalangeal joint. Sections of index finger showed typical squamous cellular cancer.

IX.—Personal communication from Dr. L. L. McArthur of Chicago, dated April 26, 1907. Patient was the first photographer to develop X-ray plates in America. "He early developed the chapped and fissured hands which go with the exposure to the ray, especially in those who combined the development of their plates with their X-ray work. For the last three years he has been having, from time to time, minor surgical procedures in the way of removal of a phalanx now and then, until three fingers of the right hand and two on the left had been sacrificed. After various plans of local treatment and a trip to Europe in search of medicinal agents, he came to me for the first time with an enormous axillary involvement. This was indubitably squamous cellular carcinoma. The radical operation with removal of portions of the pectorals and a dissection of the axilla en bloc failed to arrest the growth. Recurrence took place very promptly, and within three months again filled the axilla and involved the supraclavicular glands. Deeming it hopeless to subject him to further surgical interference, trypsin injections were given, with a resulting liquefaction of the axillary mass to a noncoagulable, sero-sanguinous fluid containing immense masses of epithelial cellular detritus, as was shown on opening and draining the sac.

After lingering for six weeks he finally succumbed to a multiple metastasis on April 23, 1907."

X.—"The second case was that of a physician who combined his electrical therapeutics from his static machine with the taking of pictures of his surgical cases. He, too, developed his own plates and constantly had his hands stained with the photographing solutions. He had the usual history of a chronic dermatitis with ulcerative processes that refused to heal, and required removal of the terminal phalanges on his left index and middle fingers. When he came to me it was with a typical epithelioma on the remains of the left index finger, and numerous scutell keratoses on the back of both hands. I amputated the finger, which microscopic section demonstrated to be carcinomatous. I removed by a deep slitting-like cut the scutell keratoses and grafted the same. I secured primary union in the grafts, had a mild infection along the suture line in the amputation and an aseptic result in the axilla which I cleaned out radically though no glands were distinctly palpable at the time of the operation. No metastases were found in those lymph glands removed from the axilla which were examined. At present he is in good health."

From a careful search through the literature and some personal inquiry these ten cases of undoubted X-ray cancer are all which I have been able to find. I have purposely excluded a few recorded cases of carcinoma developing in lupus tissue after Röntgen treatment, and one or two cases of epithelioma, following burns, for I wish to limit the question under discussion to cancer resulting in the X-ray operators who for years have followed their work in spite of previous inflammations of the skin and persistent lesions.

If my case be included, there are eleven cases, of which five have proved fatal, and as one of Siek's, reported in 1903, had to submit to a shoulder joint amputation, it is probable that this result was also a fatality. The prognosis in X-ray cancer would therefore appear appalling if it were not for the very great likelihood that all fatal cases have been published while no record has been made of the much larger number of sufferers, who after excisions or minor amputations have as yet shown no evidence of recurrence. Though it is obvious that surgeons will very naturally hesitate, in the case of a brother physician, to add publicity to misfortune, there are so many unfortunates throughout the country, suffering from chronic lesions of all grades of severity, that it is now a duty

I think for all who have charge of these cases to publish their experiences in order that our knowledge of this difficult subject may be increased.

The case which I have to report is that of an X-ray operator, who, as a young man, first began X-ray work with a large static machine in March, 1896; after October of the same year a powerful twelve-inch coil was used. Exposure lasted for several hours each day, at a very short distance from a low vacuum tube. About the middle of November blisters became red and dry, and in a few days very painful and greatly swollen. Under black-wash the dermatitis subsided, but the finger nails first became dry and striated, then softened and finally sloughed off (the patient felt convinced that this condition of the nails was greatly aggravated by the use of chromic acid in development of the X-ray plates). In spite of the fact that one per cent, orthoform ointment had to be used almost continuously to relieve the intense pain, work was continued until April 1, 1897, when the onset of another very severe dermatitis, with the formation of enormous blisters, and pain "beyond description," necessitated ward treatment for a month. White-wash gave considerable relief. All forms of treatment by ointments, powders, and washes, which Prof. J. C. White could suggest, proved useless; the chromic ulceration which now involved most of the backs of the fingers of both hands refused to heal. Orthoform ceased to relieve the pain. At the suggestion of the patient Reverdin grafts were applied on July 10, 1897, to the tip of the left forefinger, which presented the appearance of a sluggish ulcer, with rather exuberant granulations and unhealthy-looking edges. These pin-point grafts "took" and grew. Accordingly on August 13, 1897, under ether, all the ulcerated areas were cleaned up, shaved down to an apparently normal base, and Thiersch-grafted; fourteen different grafts being applied. Contrary to all expectations, the great majority of these grafts adhered and "have never broken down since, nor do they show the erematous condition, which now exists on the areas not grafted." "Pain ceased absolutely from the time of operation, and areas then grafted are in good condition to-day." "Epithelioma has never developed in any graft which completely took at this time." (I quote from a letter which the patient wrote me in 1905.)

Though all X-ray work was stopped for a year ulcers developed upon the fingers, and again in spite of all treatment refused to heal until excision with skin-grafting was carried out; after several operations all the chronic lesions were successfully grafted or healed spontaneously, except some very persistent ulcers on the ends of the ring fingers of both hands and the little finger of the right hand, which in spite of six or seven operations refused to heal.

In July, 1902, the persistent ulcerations at the tip of the ring fingers were again excised and grafted. The grafts did not take. The specimen sent to the pathologist were misplaced and not until October, 1902, was the report received that both ulcerations showed unmistakable evidence of carcinoma. In the meantime these finger tips had become excessively sensitive and painful and showed an angry-looking ulcer, with somewhat raised and indurated edges. On or near October 31, 1902, both of the ring fingers were amputated at the knuckles.

- I. The ulcer on a ring finger is shown in Fig. 1.
- II. The gross appearance under a low power in Fig. 2.
- III. The microscopic picture in Fig. 3.

During the period from October, 1902, until June, 1905, a dozen or more operations under ether were performed—amputation of the middle finger of the left hand, removal of the tips of the second and third fingers of the right hand, and numerous excisions of keratotic areas or chronic ulcerations on the dorsum of the remaining fingers or backs of the hands. Figs. 4 and 5 show the conditions of the hands.

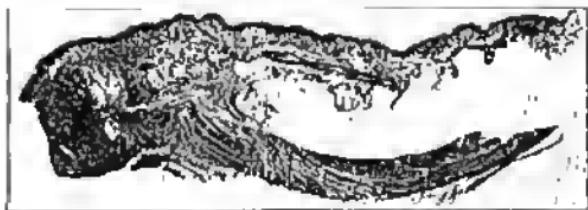
In June, 1905, for the first time in eight years, the patient was free from pain and no dressings had to be worn. Both hands could be placed in his trouser pockets. The left hand was soundly healed; the right showed one superficial ulceration at the base of the third finger, with considerable thickening of the skin about it and numerous other keratotic areas. Unfortunately during the summer the favorable condition did not endure, but steadily, though slowly, several places on both hands began to break down. Under date of November 8, 1905, the following notes were made: "For three months following a slight bruise and subsequent infection, there has been a great deal of pain in the tip of the stump of the little finger on the right hand; gradually an ulcer formed,

FIG. 1.



Cleft at end of amputated ring finger, 1902.

FIG. 2.



Ring finger, 1902. Low power.

FIG. 3.



King finger, 1902. High power.

FIG. 4.



Condition of hand, June, 1905.

Fig. 5



Condition of hand, June, 1905.

FIG. 6.



Thermal cool of little finger, Nov., 1933.

FIG. 7.



Keratoses on back of hand. Callus at base of middle finger. Nov., 1933.

about the size of an old-fashioned three-cent piece, which looks very angry and resembles those found in the ends of the fingers in 1902."

Figs. 6 and 7 show the condition. At operation the end of the little finger was removed and a suspicious ulceration at the base of the third finger thoroughly excised. The back of the forefinger over the second phalanx showed a superficial unhealthy-looking ulceration which involved the old graft; on the ulnar side of this finger were several macerated warts, which had been excessively sensitive and painful. On the radial side were numerous cracks and fissures, with some keratoses, but nothing suggesting anything malignant. All these lesions were excised, as were seven other places on the backs of the hands and Thiersch grafts were applied. All of these grafts took except those on the back of the forefinger, which sloughed and left exposed the white and glistening but not mortiferous aponeurosis of the extensor tendons. Dr. Wright's examinations showed that the ulcer on the end of the little finger was not malignant, but that the specimen removed from the base of the third finger was a typical epithelioma. One or two others suggested beginning cancerous degeneration.

During the winter and spring of 1906 these areas broke down further, and the middle joint of the first finger, from sloughing of the extensor tendon became flexed and discharged synovial fluid. For a time there was some infection, but this soon passed away. During the summer the patient suffered much from this persistent ulceration. The back of the middle finger also began to break down.

In November, 1906, under ether, the ulceration and unhealthy granulations on the back of the first finger were again excised. Examination by Dr. Wright of frozen sections showed epithelioma, or at all events invading epithelium; accordingly the excision was extended into apparently sound tissue at the margins, and the base was removed down to the bone. The dorsum of the third finger was thoroughly scraped with the knife, the tip of the little finger of the left hand removed for persistent ulceration, and several suspicious areas excised. All open surfaces were grafted successfully except the backs of the second and third fingers. A subsequent report from Dr. Wright confirmed his diagnosis of superficial epithelioma in the tissues

removed from the back of the forefinger; the ulceration on the third finger was negative.

By January 1, 1907, there was some evidence of healing from the edges in both ulcerations. The patient wished very much to delay radical treatment of the first finger, for as the thin finger was stiff, amputation meant almost total disability of the right hand.

The condition of the hands on April 25, 1907, is shown in Figs. 8 and 9—the result of ten years of treatment and twenty-five operations under ether.

On the left hand the thumb is sound and serviceable. The forefinger is stiff, but shows no lesions. The third and fourth fingers have been amputated. The little finger lacks a terminal phalanx. On the back of the hand there are a few keratoses, but no ulcerations. On the right hand the thumb is useful, but at its base is a small ulceration, and the whole ulnar side is covered with thickened epithelium. The forefinger is flexed and presents an ulceration over its middle which is undoubtedly malignant. (This finger will be amputated in June.) The middle finger is stiff. There are a few sluggish granulating areas on the dorsum, but these are healing in. The fourth finger is lacking, as is also the end of the fifth. There are numerous keratoses, but no other ulcerations on the back of the hand.

The palmar surface of both hands is normal. The skin grafts, which are outlined in black, are soft, movable, and some of the thicker ones have almost the appearance of normal skin.

The axillary glands have been somewhat enlarged for many years, but show no evidence of increase in size.

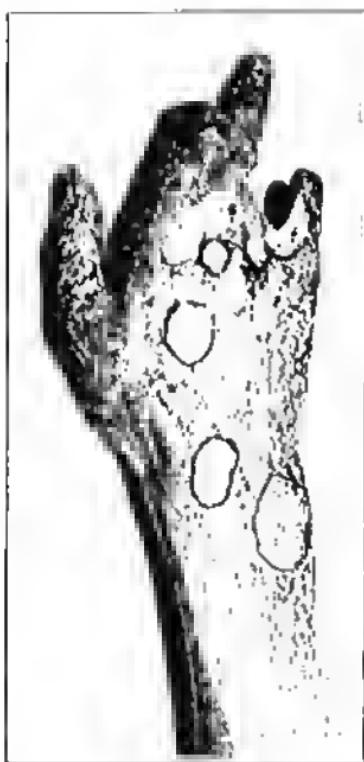
From the first demonstration of epithelial cancer in 1902 on the tips of the fourth fingers, undoubted malignant degeneration has been found in eight other areas, so that we have the extraordinary development of ten different epitheliomas in one case in five years. As the report by Dr. White will show, from such a condition there are all grades of what might be termed precancerous changes, down to simple ulceration or benign keratosis. In this as in the other reported cases, persistent ulceration has for a time, from three to six months, always preceded cancer.

FIG. 8.



Condition of hand, April, 1907.

FIG. 9.



Condition of hand, April, 1907.

FIG. 10.



Hannaford, May, 1967.

Fig. 11.



Hand of G. April, 1907.

In addition I will report a second case of chronic but much less severe dermalitis to show the advantage of skin grafting for recurring fissures; and the report of Dr. Mallory upon the recurrent growth which may prove to be a sarcoma.

Mr. J. G., X-ray operator, has suffered for many years with the milder varieties of X-ray lesions such as atrophy of the sweat glands, more or less persistent eczema, marked atrophy and longitudinal ribbing of the finger nails, with the characteristic X-ray telangiectases and keratoses. During the winter most painful fissures occurred over the extensor surfaces of the joints. It is of interest to note that none of these lesions are present over the proximal phalanx of the ring finger, which was protected from all early exposures by a broad gold ring.

In May, 1906, the keratoses and fissures on the back of the right hand were excised and grafted. Fig. 10 shows condition ten days after the operation. All of the grafts took. These were prominent and raised above the surface for a month, but at the end of that time were level with the surrounding skin and remained solid until September 15, when a spot on the terminal phalanx of the ring finger became ulcerated. Under gas and ether on October 18 this ulceration was freely excised and the radial fourth of the nail with its matrix extirpated. The skin at the margin of the nail was approximated with plaster and another graft was applied. In ten days the wound was completely healed and free from pain. This finger remained painless and healed until the middle of March, 1907, when the distal part of the graft on the radial side began to increase in size and show well-marked vascularity. After two weeks there was a slight discharge near the edge of the nail.

Examination by Dr. Wright of this specimen led him to make a diagnosis of spindle-celled sarcoma, though by some the growth was thought to be a granuloma.

By April 23, 1907, the growth had become appreciably larger and was apparently extending backward into the proximal graft. See figure 11. After careful consideration of the possibility of the return of the growth excised in October, but chiefly influenced by the anatomical conditions, which could not, in all probability, be rectified by removal of the nail and grafting, the

terminal joint was amputated under gas and ether. The wound was completely healed in a week.

Examination of tissue from finger of J. G. following exposure to X-rays by Prof. Mallory, of Harvard Medical School.

The section shows an oval, cellular mass of tissue partially surrounded by more or less normal fibrous tissue. The cellular mass at its outer end is ulcerated and covered with fibrin, cells and dead necrotic tissue. The more normal tissue is covered with epidermis. The oval, cellular mass of tissue is quite sharply defined and is limited by a layer of dense, fibrous tissue. It is composed of rapidly growing connective tissue cells and of a small number of thin-walled blood vessels. The connective tissue cells are typical; that is, they have flat, oval nuclei and contain one to three coarse chromatin masses. The cytoplasm is made out with difficulty. In places the cells are bordered by very delicate fibroglia fibrils. Everywhere the cells are separated from each other by a relatively large amount of ordinary (collagenous) fibrils. The cells and their fibrils tend to form small lamellae which run in all directions. Mitotic figures are numerous, one to three showing in nearly every oil immersion field. While the cellular mass of tissue at its base is sharply defined, on both sides, it gradually blends with the adjoining connective tissue.

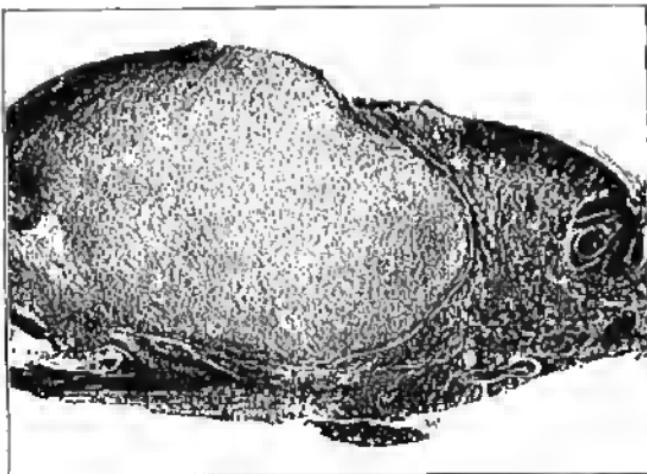
The adjoining tissue of the finger shows infiltration with numerous groups of lymphocytes. Otherwise there appears to be no change in it. It is difficult to give a positive diagnosis in this case. The rapidly growing mass of connective tissue may be either an unusual form of reparative action on the part of connective tissue or it may be a connective tissue tumor growing, namely, a rather slow growing spindle-cell sarcoma. Personally I favor the former view owing to the lack of any definite evidence as yet of invasion.

F. B. MALLORY.

The microscopic appearances under the low and high power are shown in Figs. 12 and 13. Note beginning epithelial infiltration at the extreme right of the photograph.

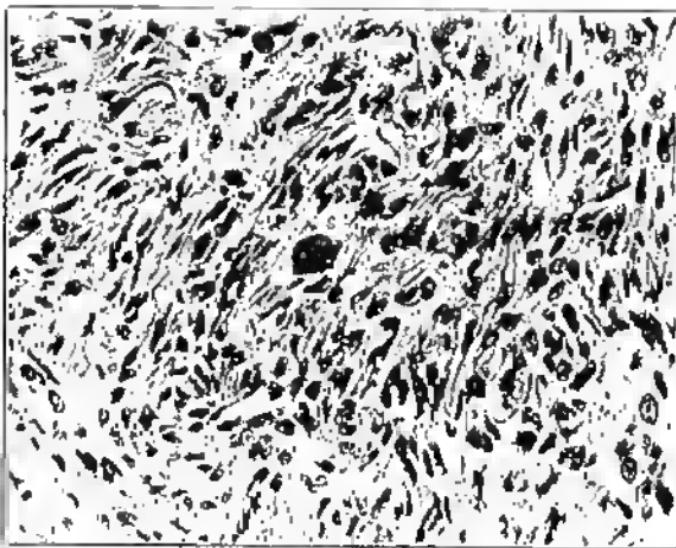
During my long experience with the first case I have learned many things about skin grafting, and now have no hesitation in recommending it, as the best treatment for all chronic X-ray lesions. Early in the history of this case, the tissues were remarkably vascular. There frequently occurred little hemorrhages in the skin, which were often the starting-point of subsequent ulceration; there appeared to be an almost complete vaso-motor paralysis. Owing to the chronic eczema no adequate disinfection was possible so that most of the early

FIG. 12.



Tissue from head of *G.* (Low power. April, 1927.)

FIG. 15



Same as Fig. 12. High power.

operations were somewhat influenced by sepsis, yet in spite of this the grafts often look surprisingly well. Haemorrhage proved to be most troublesome, not only at the time of operation, but subsequently, when blebs would form under the grafts, and unless speedily snipped with scissors would detach them. Haemorrhagic infiltration of the grafts was often noticed on the second or third day, doubling their thickness.

As a rule I applied a finger tourniquet before excising, as much of the work had to be done with great care, especially when dealing with a suspicious ulceration over an aponeurosis or tendon sheath. Fortunately, no deep infiltrations have yet occurred. After excision firm pressure by gauze was applied to the raw surfaces for ten minutes, and the hands were then exposed to the air and held aloft. No grafts should be applied until all bleeding has ceased. So far as possible an attempt should be made to level the edges of the wound. After shaving off granulations to get a smooth surface, the base of the wound is next examined for vascularity, in order to determine the thickness of the graft which should be used. While the ultimate result, if successful, which a thick graft gives, is most desirable, I feel sure that I have occasionally jeopardized healing by attempting to place a thick graft upon a very small spot, or upon such bloodless tissues as the backs of the fingers. I now use thinner grafts. If these fail, another operation should be done when the surface has become covered with granulations. A very small spot upon the fingers is most difficult to graft. I have had the best results by cutting a special graft for each place, thickest in the middle and gradually thinning towards the periphery, in order that it may fit evenly into the concavity of the wound. When possible, the whole forearm was firmly fixed with adhesive plaster to a well padded palmar splint before any of the grafts were applied. More than once from a sudden movement of the patient or an assistant, many of the grafts have been brushed off. The patient should be kept under full surgical anesthesia until the dressing is completed.

After having tried all the methods of dressing the

grafts with which I am familiar, I have adopted the following technique, and after-treatment. The grafts are so cut and arranged that they *do not overlap* either the edges of the wound or each other. If on the back of the hand, they are covered with a piece of rubber protective tissue which extends not more than $\frac{1}{8}$ of an inch beyond their edge; if on the fingers, narrow strips of protective, arranged in an imbricate fashion, encircle $\frac{2}{3}$ of the finger, and are stuck in position with blood, which soon coagulates. A small absorbent gaunce pad is then placed over the protective and then *direct downward pressure* is applied by a piece of gaunce or bandage, which is tied with a surgeon's knot on the palmar side of the splint. I was forced to resort to this maneuver by the discovery that the smaller grafts now and then were carried from left to right by the ordinary application of the bandage. Owing to the amount of exilation which occurs immediately after the operation, I have found it unwise to adopt immediate exposure to the air, as is now customary in *normal* skin-grafting. After twenty-four hours, with the hand continuously elevated, the protective is carefully removed. Longer delay in this case has almost always been followed by maceration of the grafts.

At the first dressing, blebs, if present, are snipped with the scissors and their contents gently expressed. Any lateral movement of the graft must be avoided. All the edges of the individual grafts are then greased with lanolin, or with the following ointment which was found to be less macerating.

Benzoinated lard.....	175
Lanolin	25
Schilyol	4
Silver nitrate.....	1

The grafts were then covered with a cage and allowed to dry, exposed to the air, and so treated for the next week whenever possible. Often, however, the sensitiveness and pain after half an hour's exposure were so great that the whole surface had to be covered with the ointment.

Almost without exception the pain in these ulcerated areas as well as in the X-ray burns which I have excised, has ceased from the time of operation. It is interesting to note that in one instance thick grafts grew even on the base of an epitheliomatous ulcer, but within three weeks became excessively hypertrophic. After subsequent amputation of the finger, sections showed carcinoma invading the bottom of the edematous graft.

Though future events may prove that my treatment of this patient has been too conservative, his present condition would seem to justify it.

In order that the abundance of material which has resulted from all these operations may prove of value to dermatologists, interested in the study of the pathological conditions induced by the X-rays, Dr. C. J. White has kindly made a careful examination of all the slides which have been preserved, and his exhaustive report forms a most valuable addition to my paper.

The clinical appearances of the chronic X-ray dermatoses, suggest a precocious and extreme senility of the skin; microscopic examination, also, shows the most extraordinary changes, always of a degenerative character, unequalled in their severity and chronicity by the effects of any other agent.

In view of these facts and the histories of the eleven cases reported, I think the following conclusions are justified:

1. For the atrophic condition of the skin and the telangiectases nothing can be done.
2. Hypertrophic changes, keratoses and warts may with safety be treated in the usual manner. If such treatment fails, excision with or without skin grafting, will probably relieve the pain and result in a cure.
3. Excision and grafting will prove to be the best treatment for recurrent fissures.
4. All ulcerations, which, under ordinary treatment, remain open, after three months, should be thoroughly excised, and very carefully examined. The subsequent treatment de-

pending upon the result of the microscopic examination, should be skin grafting; further excision and grafting, or amputation.

5. As the history of almost all of these cases of severe and chronic dermatitis dates back to early exposures, with the protection which our present knowledge demands, it is to be hoped that the number of victims of too enthusiastic work in an untiring field, will steadily diminish.

6. In the meantime, I have no hesitation in recommending the *early excision* of all *persistent X-ray ulcerations*, in order that subsequent malignant degeneration may be prevented.

PATHOLOGICAL REPORT.

BY CHARLES J. WHITE, M.D.,

Instructor in Dermatology in Harvard University.

The pathological report which follows is based upon the study of forty-three microscopic slides presented by Dr. Porter. The sections were already stained, for the most part by the haematoxylin-eosin, iron-haematoxylin and methylene blue-eosin methods. It is to be regretted that no fresh material was at hand for the special staining of connective tissue and elastic fibrils. The first sections date from July 17, 1902, and were as follows:

1. *Finger of Right Hand.*—Keratosis moderate. Rete somewhat hypertrophic and shows an increased tendency toward downward proliferation. Corium normal and presents no marked signs of inflammation. The deeper horizontal vessels, however, exhibit sections changes. In places veins appear displaying extraordinary mural thickening. No interior alterations are present beyond a slight enlargement of the cells but the outer coats are greatly hypertrophied. Here and there arteries are totally obliterated by endothelial overgrowth.

2. *An Ulcerated Area.*—The rete, where existent, is totally abnormal. The stratum corneum consists of a few lamellae of non-nucleated cells. The stratum granulosum is absent. The stratum spinosum is made up of greatly dilated cells, the extra-nuclear protoplasm being much rarefied and the nuclei shrunken, intravily placed, or entirely gone. The palisade layer, however, shows comparatively normal elements. Here and there are masses of red blood cells, suggesting golden pigment granules and filling the whole depth of the rete.

As the ulcer is approached the spinous cells show more distinct